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TRIAL DESIGN

Evaluation of the effects of sodium–glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial

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Background The principal biological processes that characterize heart failure with a preserved ejection fraction (HFpEF) are systemic inflammation, epicardial adipose tissue accumulation, coronary microcirculatory rarefaction, myocardial fibrosis and vascular stiffness; the resulting impairment of left ventricular and aortic distensibility (especially when accompanied by impaired glomerular function and sodium retention) causes increases in cardiac filling pressures and exertional dyspnoea despite the relative preservation of left ventricular ejection fraction. Independently of their actions on blood glucose, sodium–glucose co-transporter 2 (SGLT2) inhibitors exert a broad range of biological effects (including actions to inhibit cardiac inflammation and fibrosis, antagonize sodium retention and improve glomerular function) that can ameliorate the pathophysiological derangements in HFpEF. Such SGLT2 inhibitors exert favourable effects in experimental models of HFpEF and have been found in large-scale trials to reduce the risk for serious heart failure events in patients with type 2 diabetes, many of whom were retrospectively identified as having HFpEF.

Study design The EMPEROR-Preserved Trial is enrolling ≈5750 patients with HFpEF (ejection fraction >40%), with and without type 2 diabetes, who are randomized to receive placebo or empagliflozin 10 mg/day, which is added to all appropriate treatments for HFpEF and co-morbidities.

Study aims The primary endpoint is the time-to-first-event analysis of the combined risk for cardiovascular death or hospitalization for heart failure. The trial will also evaluate the effects of empagliflozin on renal function, cardiovascular death,

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all-cause mortality and recurrent hospitalization events, and will assess a wide range of biomarkers that reflect important pathophysiological mechanisms that may drive the evolution of HFpEF. The EMPEROR-Preserved Trial is well positioned to determine if empagliflozin can have a meaningful impact on the course of HFpEF, a disorder for which there are currently few therapeutic options.

Keywords Heart failure • Diabetes • SGLT2 inhibitors • Trial design

Introduction

The two primary phenotypes of chronic heart failure are heart failure with a reduced ejection fraction (HFrEF) and heart failure with a preserved ejection fraction (HFpEF).[1] The principal biological processes that characterize HFrEF are cardiomyocyte loss and stretch; the resulting enlargement of the left ventricle promotes the activation of neurohormonal systems that cause sodium retention, systemic vasoconstriction and adverse chamber remodelling, leading to further cardiomyocyte loss and systolic dysfunction.[2,3] In contrast, the principal biological processes that characterize HFpEF are systemic inflammation, epicardial adipose tissue accumulation, coronary microcirculatory rarefaction, myocardial fibrosis and vascular stiffness[2–6]; the resulting impairment of left ventricular and aortic distensibility (especially when accompanied by impaired glomerular function and sodium retention) causes increases in cardiac filling pressures and exertional dyspnoea despite the relative preservation of left ventricular ejection fraction (LVEF).[7] The systemic inflammation in HFpEF can also cause changes in mitochondrial function and in the mass and composition of skeletal muscle,[8] which can contribute to exercise intolerance in this disorder.

The treatment of HFrEF is primarily directed towards interference with deleterious neurohormonal systems (i.e. sympathetic nervous system, renin–angiotensin system, aldosterone and neprilysin) that are responsible for adverse cardiac remodelling. Pharmacological blockade of these pathways has been shown to reduce morbidity and mortality in large-scale randomized controlled trials.[9] In contrast, therapeutic interventions that can successfully ameliorate the derangement of biological pathways in HFpEF are still being explored. Mineralocorticoid receptor antagonists and neprilysin inhibitors have been shown to have favourable effects on cardiac structure and function and may potentially reduce the risk for serious cardiac events in these patients,[10–12] but the evidence to date is inconclusive.

Sodium–glucose co-transporter 2 (SGLT2) inhibitors were developed originally as antihyperglycaemic drugs. However, independently of their actions on blood glucose, these drugs exert a broad range of biological effects (including actions to inhibit cardiac inflammation and fibrosis, as well as to antagonize sodium retention and improve glomerular function) that position them to interfere with the principal pathophysiological derangements in HFpEF.[13–17] SGLT2 inhibitors exert favourable effects in experimental models of HFpEF[18] and in large-scale trials have been found to reduce the risk for serious heart failure events in patients with type 2 diabetes,[19–22] who are prone to develop HFpEF.[23,24]

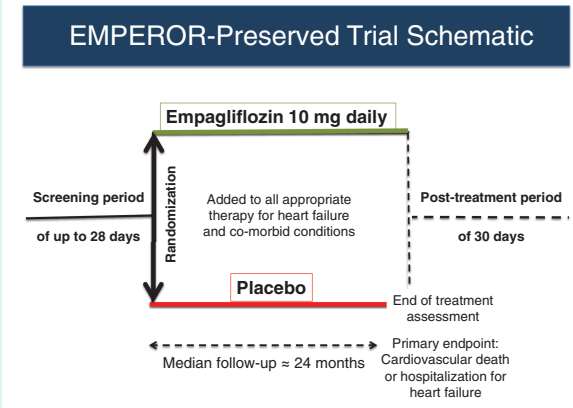

Figure 1 Design for the EMPEROR-Preserved Trial.

Therefore, SGLT2 inhibitors may represent an important advance in the treatment of HFpEF, either alone or in combination with mineralocorticoid receptor antagonists and neprilysin inhibitors, if the latter classes of drugs prove to be effective in this disorder in ongoing trials (*Figure 1*).

We are evaluating the effects of empagliflozin in two large-scale clinical trials, one focused on patients with a preserved ejection fraction (EMPEROR-Preserved, NCT03057951) and the other focused on patients with a reduced ejection fraction (EMPEROR-Reduced, NCT03057977). The two trials, taken together, constitute the EMPEROR Program. This paper describes the intent and design of the EMPEROR-Preserved Trial.

Trial structure and oversight

The EMPEROR-Preserved Trial is a Phase III international, multicentre, randomized, double-blind, parallel-group, placebo-controlled trial that is evaluating the effects of empagliflozin on morbidity and mortality in patients with established HFpEF, with or without type 2 diabetes. The trial is being carried out in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The conduct of the study is approved by an institutional review board for each participating centre, and all participants provide written informed consent before study entry. The registration identifier on clinicaltrials.gov is NCT03057951. The sponsors of the trial are Boehringer Ingelheim (Ingelheim, Germany) and Eli Lilly and Company (Indianapolis, IN, USA).

The trial was designed by the study's Executive Committee, the members of which include academic investigators, as well as representatives of Boehringer Ingelheim. The Executive Committee was responsible for the development of the study protocol and had scientific oversight on the development of the case report forms and statistical plan. In addition, the Executive Committee is overseeing the pace of recruitment, the appropriateness of the patients enrolled, and the quality and thoroughness of follow-up. The decisions and recommendations of the Executive Committee are reached through collaboration and by consensus. National leaders from key countries play major regional roles in encouraging recruitment and maintaining the commitment and dedication of investigators. A further committee, the Endpoint Adjudication Committee, is evaluating all reported and potential clinical events while blinded to the treatment assignment; these events will be judged to have met (or not met) prespecified criteria for a prespecified endpoint or safety event. An independent committee, the Data Monitoring Committee, is responsible for ongoing evaluation of the data that accrue during the course of the trial and is charged with making recommendations about the continuation or termination of the trial. At a planned interim analysis, the Data Monitoring Committee may recommend that the trial is stopped because it indicates overwhelming efficacy, which will be guided by prespecified stopping boundaries. The members of the trial committees are listed in *Appendix 1*.

Study patients

Participants in the EMPEROR-Preserved Trial are men and women, aged ≥18 years, who have had chronic heart failure (functional class II, III or IV) for at least 3 months and in whom LVEF is >40% at its most recent assessment prior to enrolment and in whom no prior measurement of ejection fraction of ≤40% is recorded. Patients are required to have elevated N-terminal pro brain natriuretic peptide (NT-proBNP) levels (i.e. >300 pg/mL in patients without atrial fibrillation and >900 pg/mL in patients with atrial fibrillation) and to show evidence of structural changes in the heart (as evidenced by increases in left atrial size or left ventricular mass) on echocardiography or a documented hospitalization for heart failure within 12 months of screening. The dose of oral diuretics must be stable for 1 week prior to randomization.

Patients are excluded if: (i) they have a cardiovascular disorder or are receiving treatments that increase the unpredictability of or may change their clinical course, independently of heart failure; (ii) they have an untreated or undertreated cardiovascular condition that may influence the course of heart failure or tolerability of the study medications; (iii) they have a significant co-morbid condition that may influence the clinical course, independently of heart failure, or (iv) they have any condition that may jeopardize their safety, limit their participation in the trial or undermine the interpretation of trial data. All exclusion criteria are listed in *Table 1*.

Study visits and follow-up

Following a screening period lasting 4–28 days, patients who fulfil all eligibility criteria are randomized in a double-blinded manner (in a 1:1 manner) to receive placebo or empagliflozin 10 mg/day, in addition to their usual therapy for heart failure. The dose of empagliflozin for this trial was selected based on the observed reduction in the risk for cardiovascular death produced by a dose of 10 mg/day in a large-scale trial in patients with type 2 diabetes (*Figure 1*).[25]

Randomization is performed by using a permuted block design with a computer pseudo-random number generator and an interactive response technology system. Randomization is stratified by: (i) geographical region (North America, Latin America, Europe, Asia, other); (ii) status of diabetes at screening; (iii) estimated glomerular filtration rate (eGFR) [Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)] of <60 or ≥60 mL/min/1.73 m,^{2} and (iv) pre-randomization LVEF of <50% or ≥50%. It is expected that approximately half of the patients will not have diabetes at the time of enrolment. Following randomization, any and all appropriate treatment for heart failure or any other medical condition or co-morbidity may be initiated, adjusted or altered at the clinical discretion of each patient's physician or health care provider according to each patient's needs, except that open-label use of SGLT2 inhibitors is prohibited.

Patients will be evaluated periodically at prespecified study visits. These assessments will include a description of the patient's New York Heart Association functional class, as well as the reporting of adverse events. Quality of life related to heart failure will be evaluated using the Kansas City Cardiomyopathy Questionnaire at randomization, after 3, 8 and 12 months of double-blind treatment, and at the end of double-blind treatment. Various biomarkers and end-organ functional assessments will include (but not be restricted to) the periodic measurement of glycated haemoglobin, NT-proBNP, renal function (including eGFR and urinary albumin-to-creatinine ratio) and liver function tests; blood samples will be banked for future biomarker analyses.

Investigators are expected to meticulously document all relevant clinical events that occur from the time of randomization until trial completion. All randomized patients will be followed for the occurrence of prespecified primary and secondary outcome events for the entire duration of the trial, regardless of whether they are taking their study medications or are fully compliant with study procedures.

Primary and secondary endpoints

The primary endpoint of the EMPEROR-Preserved Trial is the time-to-first-event analysis of the combined risk for adjudicated cardiovascular death and adjudicated hospitalization for heart failure. The primary analysis will be based on the intention-to-treat principle and include all randomized patients (from the day of randomization until the end of the planned treatment period), whether or not they continue to receive the study medications. During the trial close-out period, patients will return for an end-of-treatment visit and will be followed for an additional 30 days off treatment. Primary events occurring during this follow-up period will not be included in the primary analysis of efficacy, but will be included in a separate analysis.

Differences between the placebo and empagliflozin groups in the primary endpoint will be assessed for statistical significance using

Table 1 Exclusion criteria for the EMPEROR-Preserved Trial

Cardiovascular diseases or treatments that increase the unpredictability of or change the patient's clinical course, independent of heart failure
Myocardial infarction [increase in cardiac enzymes in combination with symptoms of ischaemia or new ischaemic electrocardiography (ECG) changes], coronary artery bypass graft surgery, or other major cardiovascular surgery, stroke or transient ischaemic attack in the past 90 days
Heart transplant or listing for heart transplant. Currently implanted left ventricular assist device
Cardiomyopathy based on infiltrative diseases (e.g. amyloidosis), accumulation diseases (e.g. haemochromatosis, Fabry disease), muscular dystrophies, cardiomyopathy with reversible causes (e.g. stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known pericardial constriction
Any severe (obstructive or regurgitant) valvular heart disease, expected to lead to surgery during the trial period
Acute decompensated heart failure requiring intravenous diuretics, vasodilators, inotropic agents or mechanical support within 1 week of screening and during the screening period prior to randomization
Implant of a cardioverter defibrillator within 3 months prior to screening
Cardiac resynchronization therapy
Untreated or undertreated cardiovascular conditions that might influence the course of heart failure or the tolerability of the study medications
Atrial fibrillation or atrial flutter with a resting heart rate of >110 bpm documented by ECG at screening
Systolic blood pressure of ≥180 mmHg at randomization. If the systolic blood pressure is 151–179 mmHg, the patient should be receiving at least three antihypertensive drugs
Symptomatic hypotension and/or systolic blood pressure of <100 mmHg at screening or at randomization
Significant co-morbid conditions that might influence the clinical course, independent of heart failure
Chronic pulmonary disease requiring home oxygen, oral corticosteroid therapy or hospitalization for exacerbation within 12 months; significant chronic pulmonary disease or primary pulmonary arterial hypertension
Acute or chronic liver disease, defined by serum levels of transminases or alkaline phosphatase more than three times the upper limit of normal at screening
Impaired renal function, defined as an estimated glomerular filtration rate of <20 mL/min/1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration) or requiring dialysis at the time of screening
Haemoglobin of <9 g/dL at screening
Major surgery (major according to the investigator's assessment) performed within 90 days prior to screening, or major scheduled elective surgery (e.g. hip replacement) within 90 days after screening
Gastrointestinal surgery or gastrointestinal disorder that might interfere with trial medication absorption
Any documented active or suspected malignancy or history of malignancy within 2 years prior to screening, except appropriately treated basal cell carcinoma of the skin, *in situ* carcinoma of the uterine cervix, or low-risk prostate cancer (patients with pre-treatment prostate-specific antigen levels of <10 ng/mL, and biopsy Gleason scores of ≤6 and clinical stage T1c or T2a)
Presence of any disease other than heart failure that results in a life expectancy of <1 year (in the opinion of the investigator)
Any condition that might jeopardize patient safety, limit the patient's participation in the trial, or undermine the interpretation of trial data
Current use or prior use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor or combined inhibitor of SGLT1 and SGLT2 within 12 weeks prior to screening or randomization. Discontinuation of a SGLT2 inhibitor or combined inhibitor of SGLT1 and SGLT2 inhibitor for the purposes of study enrolment is not permitted
Known allergy or hypersensitivity to any SGLT2 inhibitors
History of ketoacidosis
Need or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial
Current enrolment in another investigational device or drug study or completion within <30 days of a trial of another investigational device or drug study. Receipt of any investigative treatment other than the study medications for this trial
Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, will make the patient unlikely to fulfil the trial requirements or complete the trial
Pregnancy, current breast-feeding or intention to become pregnant while in the trial
Any other clinical condition that might jeopardize patient safety during participation in this trial or prevent the subject from adhering to the trial protocol

a Cox proportional hazards model, with prespecified covariates of age, gender, geographical region, diabetes status at baseline, LVEF and eGFR at baseline. Age, ejection fraction and eGFR will be included in the model as continuous variables. The most important prespecified subgroup analysis will compare the effects of empagliflozin on the risk for major cardiovascular events in patients with and without diabetes at the time of randomization.

Secondary endpoints will be analysed in a stepwise hierarchical manner in order to preserve the overall type 1 error rate at a study-wide level of 0.05 (two-sided). The first-listed secondary endpoint is the occurrence of adjudicated hospitalization for heart failure (including first and recurrent events), which will be evaluated using a joint frailty model that includes the consideration of cardiovascular death as a potential source of informative censoring. If this endpoint is successfully achieved, the analysis will proceed to an analysis of the second-listed secondary endpoint [i.e. the slope of the change in eGFR (CKD-EPI) from baseline], which will be evaluated by a random coefficient model allowing for

random intercept and random slope per patient. If the trial is not stopped at the interim analysis, an α-value of 0.001 will be assigned to the eGRF analysis and the remaining α-value will be applied to a patient-level meta-analysis, which will be prospectively carried out to evaluate the effects of empagliflozin (vs. placebo) in both the EMPEROR-Reduced and EMPEROR-Preserved Trials. The endpoints for this meta-analysis include a composite renal endpoint as well as cardiovascular death, time to onset of diabetes in patients without diabetes, and all-cause mortality; these are also designated as secondary endpoints in the individual trials. If the null hypothesis is not rejected at any step in the process of sequential analysis, subsequent hypothesis testing will be considered to be exploratory and *P*-values will be considered to be nominal. All safety analyses will be based on the treated set, which will consist of all patients who receive at least one dose of the trial medication.

Sample size calculations and study conduct

The trial will be carried out as an event-driven study and will continue until 841 adjudicated primary endpoint events have occurred, unless the trial is stopped early following a recommendation by the Data Monitoring Committee. This number of events is expected to provide the ability to detect a 20% difference in the relative risk for a primary endpoint event (two-sided), with 90% power. Based on the assumption of a 10% event rate per year in the placebo arm and a recruitment period of 18 months and a follow-up period of 20 months, we projected that the trial would need to enrol at least 4100 patients. However, in anticipation of unavoidable delays, the original protocol specified the option of increasing the number of randomized patients to 6000 if the accumulation of primary endpoint events over calendar time was slower than expected. Based on ongoing monitoring of event accrual, we reset the recruitment target at ≈5750 patients (i.e. ≈2875 patients per treatment group). The target number of patients was recalculated without any knowledge of the unblinded results of the trial and prior to the planned formal interim analysis of efficacy by the Data Monitoring Committee. Each patient will be followed for a minimum of 6 months after randomization.

Subsequent to the accrual of at least 500 primary endpoint events, the Data Monitoring Committee will carry out one prespecified interim efficacy analysis and, based on this analysis, may recommend the early termination of the study if critical *P*-values for a benefit of empagliflozin are achieved for both the primary endpoint and the analysis of cardiovascular death alone. The critical *P*-value is determined by a Hwang–Shih–De Cani α-spending function with a parameter γ-value of −8, which at approximately 500 events (60% of the total number of expected events) yields a one-sided α-value of 0.001.[26]

Discussion

A wide range of systemic inflammatory states lead to the accumulation and inflammation of epicardial adipose tissue and perivascular fat, which act as transducers for the transmission of the inflammatory process to the myocardium and aorta.[4,27,28] The inflammation of myocardial and vascular tissues causes disruption of the microvascular blood supply, cardiac and adventitial fibrosis and impaired distensibility of the cardiac chambers and great vessels.[2–6,29] The inflammatory process can also trigger the release of various cell-signalling molecules and enzymes from adipose tissue, including aldosterone, neprilysin and leptin[30]; the resulting sodium retention and expansion of plasma volume lead to a disproportionate increase in cardiac filling pressures when the left ventricle cannot expand as a result of microvascular rarefaction and fibrosis.[31] The systemic inflammatory process can also lead to renal injury (and other co-morbidities) as a result of cytokine-mediated inflammation and fibrosis of the renal parenchyma,[32,33] and renal function may deteriorate as a consequence of the glomerular hyperfiltration seen in type 2 diabetes and obesity,[33,34] which are frequently present in patients with HFpEF.

Treatment with SGLT2 inhibitors is poised to ameliorate many of the pathophysiological abnormalities seen in HFpEF.[14] In clinical trials, the use of SGLT2 inhibitors has been shown to reduce the quantity of epicardial adipose tissue (independently of effect on body weight),[35–37] and these drugs ameliorate the inflammation of adipose tissue surrounding the heart and great vessels[38,39] and the associated abnormalities of cardiac filling and aortic distensibility in both experimental and clinical HFpEF.[18,40–42] Furthermore, SGLT2 inhibitors act to inhibit sodium reabsorption in the proximal renal tubules, in which the majority of renal sodium retention occurs[43–45]; this action explains the marked reduction in plasma and/or interstitial volume and haemoconcentration seen in randomized controlled trials in type 2 diabetes.[25,46] Moreover, SGLT2 inhibitors can attenuate renal inflammation and fibrosis.[17,47,48] Additionally, the increased delivery of sodium to the macula densa that results from the inhibition of proximal tubular sodium reabsorption leads (through tubuloglomerular feedback) to a reduction in glomerular hyperfiltration, thereby ameliorating the major mechanism of glomerular injury in obesity and type 2 diabetes.[33,34,49,50] Given the multiplicity of actions on cardiac, vascular and renal pathways that are relevant to the pathogenesis of HFpEF, it seems unlikely that a benefit of empagliflozin in this condition (if found in this trial) can be ascribed solely to its diuretic effects.[46,51]

Will these actions of SGLT2 inhibitors on the heart, great vessels and kidneys lead to clinical benefits in patients with HFpEF? The ongoing EMPEROR-Preserved Trial is designed to specifically evaluate the effect of empagliflozin on the risk for cardiovascular death or hospitalization for heart failure in patients with HFpEF, as well as the drug's effect on the total number of heart failure hospitalizations. The trial is also examining the ability of empagliflozin to prevent the time-dependent deterioration of glomerular filtration, which characterizes patients with HFpEF. Importantly, because the reported benefits of SGLT2 inhibitors on heart failure do not appear to be related to their effects on glycaemic control,[25,50,51] the trial is enrolling patients with and without diabetes. Based on current understanding of its enormous range of pleotropic effects, it is not expected that the pre-treatment glycaemic status of patients will influence the magnitude or direction of the therapeutic response to treatment.

The likelihood that empagliflozin will be shown to have clinical benefits in the EMPEROR-Preserved Trial is strengthened by the fact that the drug has already been shown to reduce the risk for cardiovascular death or heart failure hospitalization and to improve glomerular function and slow the progression of renal disease in patients with type 2 diabetes, in most of whom heart failure was not identified at the time of randomization.[25,50] Although these trials did not fully characterize the phenotype of those who developed heart failure during the course of follow-up, patients with type 2 diabetes are particularly prone to the development of HFpEF.[23,24] In post hoc analyses of both the DECLARE-TIMI 58 trial with dapagliflozin and the CANVAS trial with canagliflozin[52,53] the use of SGLT2 inhibitors reduced the risk for hospitalization for heart failure in patients who were reported to have HFpEF at the time of enrolment or at the time of a heart failure event that occurred following randomization; however, these data in trials in patients with type 2 diabetes are sparse and incomplete, and thus must be considered to be hypothesis-generating. In contrast, the EMPEROR-Preserved Trial is specifically designed to determine if empagliflozin can treat patients with established HFpEF, whether or not they have diabetes. Importantly, the EMPEROR-Preserved Trial plans to evaluate a diverse array of circulating measures of adiposity and inflammation, as well as biomarkers of cardiac and renal injury. It is therefore well positioned to identify the mechanisms by which empagliflozin is beneficial if it achieves success in its planned endpoints.

Given its projected sample size of ≈5750 patients, the EMPEROR-Preserved Trial is likely to be the largest trial ever carried out in patients with HFpEF. It will provide critical insights into the pathogenesis of the disease and the mechanisms that contribute to morbidity and mortality in this disorder. It has been hypothesized that the activation of certain mediators (e.g. the leptin–aldosterone–neprilysin axis) plays an important role in the development of HFpEF in many patients.[30] Interestingly, the biological actions of the SGLT2 inhibitors evaluated in the EMPEROR-Preserved Trial can be regarded as opposite to those of leptin,[32] whereas other ongoing trials are evaluating the efficacy of inhibitors of aldosterone and neprilysin.[54,55] The totality of evidence from these trials may establish a neurohormonal basis for the treatment of HFpEF in a manner that parallels that which exists for patients with HFrEF.[14,56,57]

Conflict of interest: S.D.A. has recently received fees for steering committee activity, advisory board work and/or speaking from AstraZeneca, Bayer, Boehringer, Brahms, Novartis, Respicardia, Servier and Vifor, and has received grants for the execution of investigator-initiated trials from Abbott Vascular and Vifor. J.B. has received research support from the National Institutes of Health, Patient Centered Outcomes Research and the European Union (EU), and has served as a consultant for Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, G3 Pharmaceutical, Innolife, Janssen, LinaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, V-Wave and Vifor. G.S.F. has received steering committee fees and/or research grants from Novartis, Bayer, Vifor, Servier, Medtronic, BI and the EU. W.J., A.S., J.S., K.K., C.Z., J.G. and M.B. are employees of Boehringer Ingelheim. F.Z. has received steering committee or advisory board fees from Amgen, AstraZeneca, Bayer, Boehringer, Boston Scientific, Cardior, CVRx, Janssen, Livanova, Merck, Mundipharma, Novartis, NovoNordisk and Vifor Fresenius. M.P. has served as a consultant for Abbott, Actavis, Akcea, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Gilead, Johnson & Johnson, NovoNordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics and Theravance.

Appendix 1

Committees for the EMPEROR-Preserved Trial

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